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retinol and it is oxidated in a bi-phasic reaction system $\text{CH}_2\text{Cl}_2\text{-H}_2\text{O}$, wherein said primary oxidant is aqueous alkaline NaOCl , and wherein said nitroxyl radical is 4-oxy-TEMPO and said monomer precursor is 3-aminopropyl-trimethoxysilane to obtain a catalytic material containing chemically linked radicals, wherein said radical is tethered to said monomer precursor through reductive amination by stirring for three hours a solution of 4-oxo-TEMPO in methanol with a slight excess of 3-aminopropyl-trimethoxysilane, and reducing the thus formed imine with NaBH_3CN .

REMARKS

Paper No. 6, the Official action mailed December 14, 2001, and the prior art relied upon therein have been carefully reviewed. The claims in the application are now claims 1-11 and 13-21, and these claims define patentable subject matter warranting their allowance. Applicants accordingly respectfully request favorable reconsideration and allowance.

Applicants have claimed priority from their corresponding application filed in Italy on March 18, 1998. In addition, the PCT Branch of the PTO has acknowledged receipt of applicants' priority document, noting the Form PCT/DO/EO/903 mailed November 29, 2002. Accordingly,

applicants respectfully request the PTO to acknowledge receipt of applicants' papers filed under Section 119.

Claims 10 and 15-18 have been objected to as being in improperly multiply dependent form. This informality has been corrected above. New claims 20 and 21 replace alternatives eliminated by the corrections noted above.

Claim 12 has been rejected under Section 101 as being non-statutory. Claim 12 has now been deleted above, without abandonment of its subject matter, it being noted that process claim 13 is of substantially the same scope.

Claims 1-9 and 11-14 have been rejected under the second paragraph of Section 112. This rejection is respectfully traversed.

With perhaps a few exception and as noted below, applicants believe and submit that the claims as originally drafted, considered in light of the specification as per the law, would not be confusing to the person skilled in the art, and therefore the claims in their original form are substantially in accordance with Section 112. At worst, the criticized claims in their original form might be considered as objectionable as to form.

Nevertheless, in deference to the examiner's views and to avoid or minimize needless argument, a number of

cosmetic amendments have been made in the claims as seen in the marked up version below and as discussed below.

The amendments are of a formal nature only, i.e. made to place the claims in better form consistent with U.S. practice. Such amendments are not "narrowing" amendments because the scope of the claims has not been reduced. No limitations have been added and none are intended, i.e. the meaning of the claims has not changed.

As regards claim 1, applicants have not been able to find the word "heterogeneous" which has been criticized. The term "homogeneous" has been deleted. This is not a "narrowing" amendment, and indeed might be considered a broadening amendment.

The terminology "selected from the group including" has been changed to classic Markush language.

The term "generally" has been deleted from the expression "generally selected from ...".

New claim 19 has been added specifying that P is non-hydrolyzable, and claim 3 has been made to depend from new claim 19. This should obviate the criticism of claim 3 as lacking antecedent basis.

The examiner is correct concerning the recitation of plural ranges in a single claim, and consequently claims 4 and 5 have been appropriately amended.

The term "catalytic" has been inserted into line 2 of claim 1 so as to provide antecedent basis for claims 11 and 13. Further as regards claim 13, applicants note that antecedent basis need not be explicit; it is only necessary for the scope of the claim to be reasonably ascertainable, noting MPEP 2173.05(e) and *Ex parte Porter*, 25 USPQ2d 1144, 1145 (BPAI 1992), cited therein.

Applicants respectfully request withdrawal of the rejection.

Claims 1-9 and 11-14 have been rejected as obvious under Section 103 from Avnir et al USP 5,292,801 ("Avnir") presumably in combination with the Shames et al publication (Ref. AB of applicants' IDS and reference U on the Form PTO-892), although the combination is not made explicit in the statement of the rejection at the middle of page 4, presumably due to a clerical or data processing error.

The rejection, as understood, is respectfully traversed.

The objects of the invention claimed in the present application are as follows: One new catalytic material consisting of a sol-gel material in which the nitroxyl radicals are chemically linked to the sol-gel carrier. A sol-gel catalytic material also exists in which the nitroxyl radicals are physically entrapped in the sol-gel carrier.

This material is not claimed in that it is part of the prior art, namely Shames.

A process is claimed for the homogenous chemical preparation of both said catalytic porous materials doped with organic nitroxyl radicals, with physically entrapped or chemically linked radicals respectively, as described in general terms at page 13, lines 9-14 of applicants' specification and in detail in the examples. This process is claimed in claims 1 to 11 and specifically for the chemically linked material in claims 8, 9 and for the physically entrapped material in claim 10 respectively. This process is novel and unobvious.

A process is claimed for catalytic oxidizing in liquid phase a primary or secondary alcohol by using the catalytic materials both physically or chemically linked (claims 13 to 17).

The obviousness rejection is based on alleged obviousness, making reference to Avnir U.S. patent 5,292,801 and the Shames et al article "In situ EPR study of sol-gel processes" on Journal of Non-crystalline Solids, 175 (1994) 14-20.

Avnir describes doped sol-gel glasses. The examiner cites the example at column 6, particularly lines 9-18. The rejection states that the steps for producing the doped sol

glasses are analogous to those claimed called for in claims 1-11. The rejection also cites column 5, lines 57-68 of the same reference for the alleged obviousness of using the material to be coated as a solid support for various reagents.

Applicants strongly disagree. The non-obvious result here is that when entrapped in a sol-gel glassy matrix, an active radical is not quenched, but retains its characteristic oxidative properties contrary to what would have been expected. It is further non-obvious that such entrapped oxidant exhibits high selectivity in alcohol oxidation; that none of the doped catalysts leach out while still being accessible for reaction; and that the catalysts are recyclable. The prior art provides no reasonable expectation of any such effects, therefore the proposed combination would not have been obvious because there would have been no reasonable expectation of anything useful.

Neither Avnir nor Shames allow one to predict as obvious these results. Shames solely reports on the physical encapsulation of the 4-oxo-Tempo species in a sol-gel silica glass obtained by poly-condensation of the species TEOS followed by ESR spectroscopy in order to get information on the sol-gel process itself and on the nature of the sol-gel silica cage microenvironment.

The present invention relates to the preparation of sol-gel glasses chemically doped with the Tempo moiety radical by a process that uses 4-oxo-Tempo as suitable precursor in the presence of the species 2-aminopropyl-trimethoxysilane and TMOs, which is nowhere mentioned in the Shames et al paper nor reported in any previous work as of applicants' priority date (March 18, 1998).

Avnir covers the general preparation of sol-gel materials doped with any type of organic molecules, including enzymes. However, the simple encapsulation of an organic species within a sol-gel glass does not *per se* ensure the ability of the resulting doped glass to function as an effective chemical mediator.

Several factors must be in action to ensure such activity in the desired chemical reaction such as, among others, the polarity and flexibility of the sol-gel cages, as well as the relative stability of the material in the reaction environment of interest. Accordingly, other patents covering encapsulation and use of particular species have been granted that are not covered by Avnir, such as in the case of the sol-gel encapsulated enzymes lipases described by M.T. Reetz et al in DE 44 08 152 A1 (1994).

It is known for instance, that silica is not stable in an alkaline environment due to progressive dissolution of

the silica backbone upon attack of siloxane bonds (Si-O-Si) by hydroxyl ions. Furthermore, doped materials in oxidative environments are often unstable towards leaching of the encapsulated dopants in solution as is explained by R.A. Sheldon et al in ACC. Chem. Res., 31 (1998) 485-493.

Accordingly, and as stated in the present patent application, commercial silica Bio-Sil-NH₂ dopes with 4-oxo-Tempo employed in the NaOCl/NaBr oxidation of glucose-1-phosphate in water described by A. Heeres et al in Carbohdr. Res. 299 (1997) 2210227, lost 60% of its activity after a single oxidation run and was entirely inactive after only two more runs, showing the high instability of such a catalyst in the oxidative alkaline environment in which, by contrast, the sol-gel glasses showed stable selective activity in several consecutive oxidation runs of D-methylglucose. Such negative results in the prior art would have dissuaded those of ordinary skill in the art from even trying to do what applicants did successfully.

It is the chemical and physical nature of sol-gel glasses, along with the mild character of the oxidation carrier out at 0-4°C at pH 9.0-10, that ensures the remarkable stable activity here reported. The sol-gel caging, in particular, highly protects the radicals both chemically and physically within the cages instead of leaving them

unprotected at the surface; while the doped glass as a whole acts as a chemical sponge, adsorbing and concentrating the reactants at the pore surface.

In summary, the present invention represents the effective overlap of two different advanced and highly versatile chemical technologies (namely the sol-gel doped glasses and TEMPO-mediated oxidations) which, as explained above, was not foreseeable as being successful on the basis of the previous knowledge.

Withdrawal of the rejection is in order and is respectfully requested.

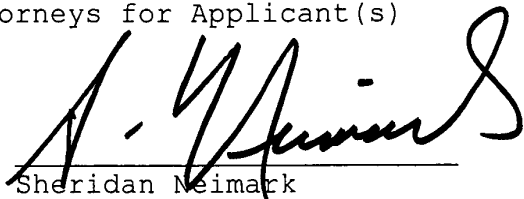
New claims 19-21 are patentable for the same reasons pointed out above.

Favorable reconsideration and allowance are respectfully urged.

Respectfully submitted,

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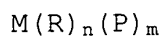
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Version with Markings to Show Changes Made

1. (Amended) A ~~homogeneous~~ process for the preparation of reactive sol-gel catalytic porous materials either chemically or physically doped with stable organic nitroxyl radicals, comprising the steps of:

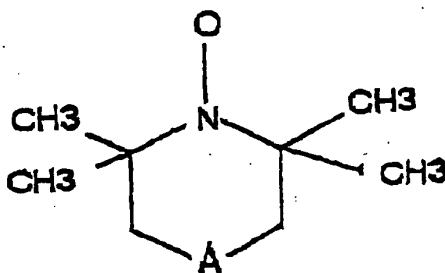
a) copolymerizing a solution including:

at least one monomer precursor selected from the group ~~including~~ consisting of metal and semi-metal alkoxides, metal esters ~~or~~ and semi-metal esters, of the general formula



wherein M is a metal or a semimetal, R is an hydrolysable substituent, P is a non-polymerizable group, n is an integer of 1 to 6, and m is an integer of 0 to 6,

a dopant consisting of a stable di-tertiary-alkyl nitroxyl radical or a precursor thereof of formula



wherein A represents a chain of two or three carbon atoms, one or two of said carbon atoms being eventually substituted by one oxygen or nitrogen atom,

a solvent including H₂O and a co-solvent generally selected from the aliphatic alcohols;

an acid or base to catalyse the processes of sol-gel hydrolysis and copolymerization; and

one or more additives selected from those known to be useful in the preparation of porous materials

to form a gel containing said dopant trapped therein;

b) evaporating said solvent;

c) drying said gel;

d) coating said gel on a mesoporous inorganic support; and

e) drying said mesoporous material coated with said sol-gel.

3. (Amended) The process according to claim ~~1~~19, wherein said non-hydrolyzable substituent is H, an alkyl, aryl or fluoroalkyl group or an aminoalkyl group.

4. (Amended) The process according to claim 1, wherein said step c) of drying the gel is a liophilisation carried out at a pressure lower than 70 mm Hg ~~and preferably 15 mm Hg~~, to obtain a mesoporous aerogel powder.

5. The process according to claim 1, wherein said step c) of drying the gel is a mild heat treatment carried out

at an atmospheric pressure and a temperature no greater than 100°C ~~lower than 100°C, and preferably at 45°C.~~

10. (Amended) The process according to claim ~~16~~, wherein said nitroxyl radical is TEMPO or a precursor thereof and said radical is physically entrapped within a sol-gel matrix adding a solution thereof in methanol to said precursor following ~~either said one- or two-step procedure as claimed in claim 6 or 7.~~

15. (Amended) A process according to claim 13, wherein said alcohol substrate is an alkyl alcohol, an aryl alcohol, a steroid alcohol, an allylic alcohol, a terpenoid alcohol or retinol and it is oxidated in a bi-phasic reaction system $\text{CH}_2\text{Cl}_2\text{-H}_2\text{O}$, said primary oxidant is aqueous alkaline NaOCl and ~~said catalytic material is prepared according to claim 8 or 9 and it is added to the reaction system under stirring~~ wherein said nitroxyl radical is 4-oxy-TEMPO and said monomer precursor is 3-aminopropyl-trimethoxysilane to obtain a catalytic material containing chemically linked radicals.

16. (Amended) A process according to claim ~~13 or 14~~, wherein said alcohol substrate is a monomer or an oligomeric carbohydrate protected at the anomeric center, said solvent is water, said oxidant is alkaline NaOCl or NaOCl in the presence of a catalytic amount of NaBr, and ~~said catalytic~~

~~materially added to the reaction solution is one as claimed in anyone of claims 8, 9 or 10 wherein said nitroxyl radical is 4-oxy-TEMPO and said monomer precursor is 3-aminopropyl-trimethoxysilane to obtain a catalytic material containing chemically linked radicals.~~

17. (Amended) A process according to claim 16, wherein said catalytic material is in the form of pumice stones coated with a said sol-gel film doped with said ~~ntroxyl~~ nitroxyl radicals, ~~as claimed in anyone of claims 1 to 10 and~~ said carbohydrate is a water soluble polymer.

18. (Amended) The catalytic material doped with a chemically linked nitroxyl radical obtained with a process as claimed in ~~anyone of claims 8 and 9~~ claim 8.